AMERICAN ASSOCIATION OF SWINE PRACTITIONERS

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April 2, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket No. 98D-1146

Dear Sir or Madam:

The American Association of Swine Practitioners (AASP) is a professional organization with a membership of over 1,200 veterinarians in the United States. AASP's members have an abiding interest in swine health and production. The issue of continued availability of effective antimicrobial for use in swine is of great importance to the AASP. The safe and effective use of antimicrobial is a critical component of maintaining a healthy and safe supply of pork for the consuming public, as well as providing for the health and well-being of the nation's swine herd.

The AASP is submitting comment in response to the discussion paper entitled *A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-producing Animals.*

The AASP recognizes and appreciates the efforts of the Food and Drug Administration (FDA) in keeping the nation's food supply safe. We also appreciate the FDA's efforts in assuring the safety and effectiveness of pharmaceuticals used in food animal medicine. The scrutiny of the FDA has been crucial in our joint efforts to provide for the health and well-being of animals. However, the AASP has significant concerns about the proposed framework.

The AASP recognizes the complexity of the issue. However, we are disappointed in the FDA's attempt to justify greater regulatory action without a more thorough effort to elucidate the scientific basis for such action. While several well publicized reviews of this issue suggest that there is reason for

98D-1146

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concern, they do not indicate there is sufficient evidence justifying a major overhaul of the drug approval process. The reviews do, however, call for more research and information.

Public health would be better served if the FDA were to propose a research agenda rather than a regulatory approach which could be construed as an application of the precautionary principle (i.e., the application of precautionary measures even when cause and effect relationships are not fully established scientifically). There is great fear in animal agriculture today over the continued availability of antimicrobial to treat food animals. Reinforcing this fear is the concern that availability maybe severely decreased with no discernible positive impact on public health. AASP will vigorously support a sound scientific and risk-based approach to evaluating and assuring the human safety of the microbial effects of antimicrobial new animal drugs for food-producing animals.

The framework proposes to manage a risk the FDA has not adequately assessed. It fails to recognize the need to separate hazard from risk. The FDA has identified a hazard, but appears to not recognize the need to evaluate risk with respect to:

1) How likely is the hazard to occur?
2) What is the magnitude of the outcome should the unwanted event occur?

The AASP agrees with the FDA that the impact of animal uses of antimicrobial drugs on human health should be reexamined. However, we disagree that the proposed framework in its present form and detail is the appropriate approach to "evaluate and minimize the potential human health effects" of such uses. The evaluation of the issue should be done within a scientific risk assessment. Risk management could then be implemented in proportion to the attributable risk.

As the document was examined for its scientific merit, immediate concerns were evident. The framework fails to adequately define many terms. This lack of clarity invites subjective and misleading interpretations. Examples of terms requiring definition include:

. pathogen load
. human health effects
- induction of resistance
- significant baseline of colonization

A referenced glossary with scientific citations would be useful to further discern the scientific basis of this framework.

Further questions of the scientific foundation of the document can be raised. The first eight references were "anonymous" and did not represent peer-reviewed science. If there is science worth citing, then it would be more convincing to cite the original peer-reviewed sources. Examination of the document reveals that the words "FDA believes" or some variant of this phrase appears 47 times. The complexity of this issues requires that belief be founded on science alone, and the document is less than convincing on this matter. AASP's minimal expectation is that the FDA would conduct a credible and

exhaustive review of the scientific literature before proposing demanding and expensive requirements.

There are examples given within the document which tend to mislead and bias the reader. One such an example is found on page 3 of the document where E. coli 0157 is highlighted as being a common intestinal flora of various food-producing animals. Research has shown it to be transient in individual animals and not a persistent colonizer. It is also recognized that human-to-human transmission does occur. Of greater concern is that the document implies that E. coli 0157, which has considerable emotive impact on the public, is pertinent to the antimicrobial resistance issue. The understanding of the AASP is that antimicrobial therapy is generally contra-indicated for treatment of E. coli 0157 infection and clinical resistance is not a primary concern.

Another biased illustration used within the document is the vancomycin-resistant enterococcus (VRE) found in Europe. VRE is of great public health importance. However, it is not relevant as an example for animal agriculture in the United States. It has no correlation to the use of antimicrobial in food producing animals in the US, since there are no glycopeptides used in US animal agriculture. The VRE problem in the US is a result of antimicrobial use in humans, not animals.

There are other instances where scientific citations would be useful. The document often associates pathogen load with duration of therapy. There are statements in the document where the use of antimicrobial (especially for a long duration) is inferred to "disturb the normal intestinal ecosystem in the animal, resulting in an increase in the bacteria that can cause human infections" or prolong the duration of "the carrier state of such bacteria (pathogen load)." In a cursory discussion, an AASP review panel identified several papers on antimicrobial use in swine that seem to contradict the position of the FDA in the document.

In general terms, the discussion on the evaluation of the potential exposure of humans centers more on the exposure of bacteria to antimicrobial than on the exposure of humans to resistant human pathogens and a subsequent clinical human health impact. The given examples base potential exposure of humans to resistant human pathogens on the duration of treatment. Once again, we ask for the scientific basis for this assumption. The use of this type of surrogate measure for human exposure may be easy, but has no potential for objectively measuring clinical significance to public health.

We agree that the effects of antimicrobial resistance transfer from animals to humans involves a complex chain of events. The document lists the ability of the drug to induce resistance; the likelihood that use in food-producing animals will promote such resistance; the likelihood that any resistant bacteria in or on the animal will then be transferred to humans; and the likelihood that such transfer will result in loss of availability of human antimicrobial therapies. We would, however, add the following:

- the likelihood that transfer will cause illness;
- the likelihood that the illness will require antimicrobial treatment; and

. the likelihood that the resistance will result in treatment failure.

These inclusions will bring the FDA closer to a true evaluation of the clinical importance of antimicrobial resistance.

The document's bias again comes through in several instances. The first arises when foodborne diseases are recognized as part of the criteria for a drug's placement into Category I. This elevates foodborne illness to the same status as "serious or life threatening disease". In fact, the vast majority of foodbome illness is not serious nor life threatening. We ask that the FDA characterize the clinical importance of treatment failure in foodbome illnesses within the context of all antimicrobial failures in human medicine. Within this more global realm, one may develop an unbiased response to the risk.

A second example of bias is found within the discussion of the example for the "high potential human exposure". The label claim of improved growth or feed efficiency is highlighted in the example and the ensuing discussion. We question how the label claims are relevant to the potential for human exposure to resistant pathogenic bacteria. If data exists to prove a link between label claims and human exposure to resistant pathogenic bacteria, then the FDA should be forthcoming and cite such data.

The AASP urges the FDA to critically consider how they can tie measurable public health outcomes to proposed thresholds. Without science to appropriately measure outcomes as related to thresholds, how do they propose risk management that will be clinically important in the protection of public health? We question the following:

. how the FDA intends to measure the rate of resistance transfer in vivo;
. what measure of resistance will be used;
. if used, how MIC's and breakpoints will be used to determine clinical human health impact; and
. what constitutes "sufficiently sensitive tests".

The AASP also urges the FDA to reveal the research that supports on-farm monitoring as a means to predict public health outcomes. We know of no scientific basis to demonstrate any quantitative or even qualitative relationship between on-farm resistance and any human health impact. Until such basis can be established, any on-farm data would be dubious in discerning any clinical importance to humans. Even worse, the on-farm data could be manipulated in a subjective manner to initiate unwarranted and politically-motivated action against particular on-farm uses of antimicrobial.

As an alternative to on-farm monitoring, the AASP supports the strengthening of the National Antimicrobial Resistance Monitoring System (NARMS) program as a better use of limited resources. The surveillance of zoonotic pathogens at the slaughter plant gives a much better picture of the hazards of bacterial contamination of meat. It places the monitoring closer to the final consumer.

In closing, the AASP urges the FDA to evaluate the risk before attempting to manage it through regulation. We urge the FDA to not yield to political expediency at the expense

of critical, scientific analysis. The AASP proposes that the FDA utilize a process not unlike the peer-review publication process employed by credible scientific journals. A rigorous scientific examination of the current science by an independent third party could provide valuable input to establishing the basis of the approval process for antimicrobial to be used in food animals.

We urge the FDA to consider an open and meaningful dialogue with outside experts and stakeholders. The AASP stands ready to participate in any and all credible efforts to assure that human and animal health and well-being are protected. The complexity of this issue should not be used as an excuse to assume a default, precautionary position that jeopardizes the future availability of antimicrobial for food animals with no assurances of any mitigation of risk to public health.

The AASP thanks the FDA for this opportunity to comment. We look forward to a continued dialogue on this critical issue.

Sincerely,

Tom Burkgren

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